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Patent Application
Attorney Docket No.PC10228A

RCE
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11/8/02

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Farzan Rastinejad et al.

APPLICATION NO.: 09/443,542 : Examiner: Dr. Jerome D. Goldberg

FILING DATE: November 19, 1999 : Group Art Unit: 1614

TITLE: METHODS AND COMPOSITIONS FOR RESTORING CONFORMATIONAL STABILITY OF A PROTEIN OF THE p53 FAMILY

Commissioner for Patents
Washington, D.C. 20231

Sir:

Request for Continued Examination ("RCE") under 37 C.F.R. §1.114(a)(2)

Pursuant to 37 CFR 1.114 (a)(2), and prior to abandonment of the application herein, Applicants respectfully request continued examination in view of the Reply filed herewith.

Authorization is hereby provided to charge the amount of $740.00 as stated under 37 C.F.R. §1.17(e), as well as any additional fees or fee amounts required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

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Respectfully submitted,

Date: 10/28/02

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Attorney Docket No. PC10228A

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail, postage prepaid, addressed to the Commissioner for Patents, Washington, D.C. 20231, on this 28th day of October 2002.

By _____
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#23 JRP 11/8/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Farzan Rastinejad et al.

APPLICATION NO.: 09/443,542 : Examiner: Dr. Jerome Goldberg

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Commissioner for Patents
Box Amendment
Washington, D.C. 20231

Sir:

Reply under 37 CFR 1.114(a)(2)

The present Reply is in response to the Official Action of April 26, 2002, made final, wherein all of the claims under examination (Nos. 26-35) were rejected. Careful consideration has been given to the Examiner's rejections. Reconsideration via this Request for Continued Examination is respectfully requested.

The Examiner has requested (see Page 2 of the Official Action) cancellation of claims 1-8, and 24 apparently since they are non-elected. However, Applicants understand that non-elected claims need not be canceled until allowance. Clarification is requested.

Currently only claims 26-35 are under consideration. Both elected compound species X and the treatment of cancer read on claim 26. No further cancellation of subject matter is appropriate at this time. The Examiner will be unable to demonstrate any prior art whatsoever for the treatment of cancer as claimed by Applicants, and thus upon indication of allowability as to species X, the generic claim should be allowed.

Claims 26-35 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that the admittedly enabling specification is not enabling commensurate in scope with the claims. The Examiner contends that the Specification "does not reasonably provide

enablement for the term 'cancer,'" reasoning that the term "cancer" "lacks clear exemplary support in the specification as filed." The Examiner further asserts that the specification "does not reasonably provide enablement for the term 'organic non-peptide compound,'" reasoning that this term"lacks clear exemplary support" and "is so broad as to include compounds that are not disclosed in the specification." The Examiner's rejections are respectfully traversed.

Applicants respectfully submit that the Examiner's position is not supported by the law. It is well-established that any assertion by the Patent and Trademark Office that the enablement of the disclosure is not commensurate in scope with the protection sought must itself be supported by evidence or reasoning substantiating the doubts so expressed. In re Dinh-Nguyen, 181 U.S.P.Q. 46, 47 (CCPA 1974); In re Bowen, 181 U.S.P.Q. 48, 51 (CCPA 1974). The Examiner has not done so. In the present case, the Examiner has proffered no evidence or sound reasoning to support his assertion that the enabling disclosure is not commensurate in scope with the protection sought, as required by the courts.

As stated in In re Marzccchi, 169 U.S.P.Q. 367, 369 (CCPA 1971:

> As a matter of Patent Office practice then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

As a consequence, it is incumbent on the PTO to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. Id. at 370; see also In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995) ("[T]he PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."). Mere allegation by the Examiner is plainly not enough.

A specification is enabling even if it requires a "considerable amount" of experimentation, as long as the experimentation is routine. Ex parte Forman, 230 U.S.P.Q. 546, 547 (PTOB 1986); see also In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). A

major factor to be considered is whether "the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claims." Forman, 230 U.S.P.Q. at 547. As will be demonstrated below, no undue experimentation is required to carry out the claimed invention.

Applicants first addresses the Examiner's objection to the term "cancer." The present invention is drawn to a method for treating a human subject for cancer comprising administering to the subject an organic non-peptide compound that is capable of binding to one or more domains of a human protein of the p53 family under physiological conditions, and stabilizing a functional conformation therein, and permitting the then stabilized protein to interact with one or more macromolecules that participate in a wild-type activity of the protein. (See, e.g., the specification at p. 13). The specification provides ample guidance to one having ordinary skill in the art to practice the claimed method of treating cancer without undue experimentation.

It is well known that many cancers are associated with conformational defects in the proteins of the p53 family, caused by, e.g., mutations in the p53 family genes. As the specification at p. 1 states, "mutants of p53 are the most common genetic aberration in cancer." This is clearly demonstrated by the following illustrative quotes from many highly respected journals:

> "The p53 guardian of the genome is inactivated in the majority of cancers, mostly through missense mutations that cause single residue changes in the DNA binding core domain of the protein." A. Signal, et al., Cancer Research 60, 6788-6793 (Dec. 15, 2000).
>
> "Perturbation of p53 protein function is a common, if not universal, finding in human cancer." W. Kaelin, Jr., Journal of the National Cancer Institute, Vol. 91, No. 7 (April 7, 1999).
>
> "TP53 is the most frequently mutated gene in human cancers and is thought to play a crucial role in malignant transformation." A. Zeimet, et al., Biochemical Pharmacology, Vol. 60, pp. 1153-1163 (2000).
>
> "Given that human cancers are biologically and pathologically quite distinct, it has been quite surprising that a common event, perturbation of the p53 pathway, occurs in most if not all types of human cancers." T. Hupp, et al., Biochem. J. 352, 1-17 (2000).

"One protein -- p53 -- plays nemesis to most cancers by condemning damaged cells to death or quarantining them for repair." A. Bullock, et al., Nature Reviews, vol. 1, pp. 68-76 (2001).

"[T]he majority of human cancers overall carry mutant p53 genes." M. Smith, et al., Cancer Biology & Therapy, Internet pre-published on Sept. 5, 2001 as Manuscript MS# 08-30-02.

"The p53 gene is lost or mutated in most human cancers." The Journal of Antibiotics, vol. 54, no. 10 (Oct. 2001).

"Mutation of p53, which is the most frequent genetic alteration detected in human cancers, inactivates these growth regulatory functions and causes a loss of tumor suppressor activity." C. Cadwell, et al., Gene 277 15-30 (2001).

"p53, perhaps the single most important human tumor suppressor, is commonly mutated in human cancers." A. Grimberg, Molecular Genetics and Metabolism 70, 85-98 (2000).

"Mutations in the p53 tumor suppressor are the most frequently observed genetic alterations in human cancer." Y. Cho, et al., Science, 265, pp. 346-355 (1994).

The present specification teaches a method of treating cancer by administering an organic non-peptide compound that is capable of binding to one or more domains of a human protein of the p53 family under physiological conditions, and thereby stabilizing a functional conformation of the protein. As the specification makes clear, the specific cancers listed in the disclosure (see p. 34-35) are merely examples of cancers associated with mutations in the p53 proteins. The specification at p. 35 expressly states that "[t]he above cancers, and others, are treatable by the methods and compounds of the invention." (Emphasis added.) The Examiner has offered no evidence that undue experimentation is required for one skilled in the art to practice the claimed method, especially in view of the broad role played by p53-type proteins in cancer.

Moreover, the PTO has consistently issued patents with claims to methods of treating "cancer" with limited support in the specification. The present specification provides very detailed support in the specification, and indeed provides first ever disclosure of a basic biological mechanism, that small non-peptide organic compounds can stabilize proteins of the p53 family to great benefit including in an ex-vivo xenograft model.

The following 25 patents are illustrative of circumstances where the U.S. Patent Office issued claims to the treatment of CANCER. It is submitted that the Examiner has misapplied the law, and that the present Applicants are entitled to equal consideration under that law. It is otherwise appropriate to immediately ask whether the Patent Office is taking the position that all of the below patents are deemed by the PTO to be invalid.

Patents	Claims to Treating Cancer	Support in Specification
6,395,771	3, 4, 11, 12	Leukemia cells, and ovarian, breast, lung, and cervical cancers. (Col. 9, 11. 30-60.)
6,403,554	25-30	General statement of cancer treatment with no examples. (Col. 2, 11. 5-10.)
6,399,638	6, 7	Laundry list of cancers and tumors (col. 5, 11. 60-67; col. 6, 11. 1-19.), with only one example of a cytotoxicity assay using coloncarcinoma cells. (Col. 36, ll. 49.)
6,399,653	13	General statement of treatment of cancer with no examples. (Col. 2, ll. 54-61.)
6,399,647	1	Human colon cancer. (Col. 34, ll. 11-49.)
6,399,583	10	Uterine sarcoma cells, Lewis lung carcinoma cells, melanoma cells, lung squamous cell carcinoma, leyding cell tumor, mouse lymphocytic leukemia cells, and P388 leukemia. (Cols. 20-22.)
6,399,598	20, 22	Premetastatic tumor. (Col. 42, ll. 43-65.)
6,403,625	6	Stomach cancer, esophageal carcinoma, duodenal carcinoma, rectum cancer with no examples. (Col. 5, ll. 47-51; col. 6, ll. 44-47.)

6,403,569	1	Colorectal cancer. (Col. 1, ll. 7-15; col. 6, ll. 7-13)
6,403,592	10	Small cell lung carcinoma with no examples. (Col. 11, ll. 59-60.)
6,406,699	1	Breast cancer, astrocytoma, renal cell carcinoma. (Cols. 11, 18, 20.)
6,395,749	20	General statement of cancer treatment with examples of human prostate cancer and an unspecified tumor. (Col. 13, ll. 61-62; col. 15, ll. 40-43; Exs. 12 and 13.)
6,384,049	1, 12	Laundry list of cancers with only one example of colon cancer tumor in mouse. (Cols. 3-5; Ex. 1.)
6,392,063	43, 44	Cancer of the brain, stomach, lung, colon, prostate, breast, ovary, head or neck, and leukemia, lymphoma, carcinoma, or sarcoma. (Col. 5, ll. 10-13.)
6,387,903	4, 5	Human pancreatic carcinoma. (Exs. 20-22.)
6,391,888	?	General statement of treating cancer, such as solid tumors and leukemia. (Col. 6, ll. 38-44.)
6,372,785	5, 8	Carcinomas, sarcomas, melanomas, and lymphomas affecting organs such as lungs, mammary tissue, prostate gland, intestines, liver, heart, skin, pancreas, and brain. (Col. 5, ll. 55-67.)
6,388,131	21	General statement of treating cancer with examples of

		human cervical carcinoma. (Col. 10, ll. 61-65; Ex. 28.)
6,391,302	1	General statement of treating cancer. (Col. 3, ll. 55-57; Ex. 2.)
6,391,913	11	General statement of cancer treatment. (Col. 2, 11. 66-67.)
6,387,673	1	General statement of cancer treatment with no examples. (Col. 6, 11. 40-45.)
6,391,853	47	General statement of cancer treatment with no examples. (Col. 2, 11. 55-64; col. 3, ll. 7-9.)
6,391,916	24, 30	General statement of treating cancer with examples of mice T leukemia cells. (Col. 3, 11. 37-40; Ex. 69.)
6,395,729	7, 13	General statement of treating cancers and tumors with no examples. (Col. 7, 11. 42-67; col. 8, 11. 1-5.)
6,359,000	1	General statement of treating cancer with no examples. (Col. 1, 11. 11-14; col. 2, 11. 44-50.)

Accordingly, Applicants respectfully submit that it is improper for the Examiner to require the claims be limited to the specific cancers listed in the specification.

With respect to the Examiner's objection to the term "organic non-peptide compound," Applicants respectfully submit that the present specification provides an enabling disclosure for one having ordinary skill in the art to practice the claimed invention. For example, the specification teaches that "[t]he organic non-peptide compounds of the invention can be any type of compound that, when exposed to a wild type or mutant protein of the p53 family, promote the wild type activity of the protein." (p. 17.) The specification (1) provides very numerous examples of organic non-peptide compounds which are suitable for the invention (e.g., pp. 18-31); and (2) discloses detailed methods to screen and to

discover additional compounds that promote a wild-type activity of a protein of the p52 family (e.g., pp. 33-40). Thus, the present disclosure provides ample guidance to one having ordinary skill in the art to select and identify the appropriate organic non-peptide compound to practice the claimed method without undue experimentation. Applicants respectfully submit that the Examiner has no contrary evidence.

Indeed, recently, others have utilized the teachings of the present pioneering invention to identify additional organic non-peptide compounds that can bind to one or more domains of a human protein of the p53 family. For example, Bykov, et al. (WO 02/24692 A1) disclose using Applicants' procedures published in Foster, et al., Science, v. 286, pp. 2507-10 (1999) to identify such compounds. (See, e.g., pp. 20-21 of Bykov, et al.)

The Examiner contends that the term "organic non-peptide compound" "can include well known anticancer agents" such as those disclosed in O'Connor, et al. However, there is no teaching or suggestion in this reference, or elsewhere in the current art, that those compounds bind to one or more domains of a human protein of the p53 family under physiological conditions, and stabilize a functional conformation of said protein, as claimed by the present invention.

The Examiner states that "the term [organic non-peptide compound] is so broad as to include compounds that are not disclosed in the specification." Applicants respectfully submit that the Examiner's attempt to limit the scope of the claims to the specific compounds disclosed in the specification oversteps the requirements imposed by 35 U.S.C. § 112. As the court explained in In re Rainer, 134 U.S.P.Q. 343, 346 (CCPA 1962):

> It appears to us that the board is here confusing the requirements for claims with the function of the specification. One does not look to claims to find out how to practice the inventions they define, but to the specification.

The statute 35 U.S.C. § 112 does not require claims to include all of the preferred features that permit the effective function of the claimed subject matter. As the CCPA further explained in In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970):

> The Examiner's approach to determining whether appellants' claims satisfy the requirements of § 112 appears to have been to study appellants' disclosure, to formulate a conclusion as to what he (the examiner) regards as the broadest invention supported by the disclosure, and then to determine whether appellants' claims are broader than the examiner's conception

> of what "the invention" is. We cannot agree that § 112 permits of such an approach to claims.

Applicants respectfully submit that in the present case, the Examiner has done exactly what the Court has cautioned the examiners not to do. The Examiner has limited the enabling scope of the instant disclosure by studying Applicants' disclosure, concluding that the broadest invention is supported only by the disclosed species/examples and the preferred embodiments, and impermissibly restricting the scope of the invention to what the Examiner regarded as Applicants' broadest invention.

It is well-established that claims need not be limited to exemplification or preferred embodiments in order to satisfy enablement requirements. See Ex parte Gould, 6 U.S.P.Q.2d 1680 (BPAI 1987). Further, an applicant need not provide a specific example of everything embraced by a broad claim and the PTO cannot attempt to "limit all claims to specific examples, notwithstanding the clear disclosure of a broader invention." In re Anderson, 176 U.S.P.Q. 331, 333 (CCPA 1973); See also In re Angstadt, 557 F.2d 498, 503 (CCPA 1976) (holding that "appellants are not required to disclose every species encompassed by their claims even in an unpredictable art . . . ."). Under the law, Applicants are entitled to claim all embodiments of an invention, including those that are not specifically disclosed. U.S. v. Telectronics Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988) ("the law does not require an applicant to describe in his specification every conceivable embodiment of the invention").

Moreover, as discussed in Applicants' Reply to Official Action dated January 14, 2002, Applicants are entitled to a broad claim because the present invention is pioneering as evidenced by its reception in the scientific community. See In re Hogan, 194 U.S.P.Q. 527, 537 (CCPA 1977) ("[P]ioneers . . . deserve broad claims to the broad concept").

Further, the PTO has issued patents with claims to compounds which can stabilize conformational defect in a protein. For example, U.S. Patent No. 6,270,954 (issued to Welch et al.) claims a method for improving the phenotypic defect in a cell that contains a conformationally defective target protein by contacting the cell with a "protein stabilizing agent" that is effective to improve the conformational defect. The specification support for the claimed term "protein stabilizing agent," however, is only a handful of compounds. (See, e.g., col. 8, ll. 29-41 of the '954 patent.)[1] In contrast, as discussed above, the instant

[1] See also U.S. Patent No. 5,900,360 (also issued to Welch, et al.) The Welch patents

specification provides substantial support for the claimed term "organic non-peptide compounds" and more than a reasonable amount of guidance to practice the claimed invention.

In view of the foregoing remarks, Applicants respectfully submit that the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is in error, and it should be withdrawn.

Conclusion

A Petition for Extension of Time (3 months) is attached in duplicate, as is a Request for Continued Examination (also in duplicate). The Patent Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Account 16-1445.

Respectfully submitted,

Date: 10/28/02

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are based on the Brown et al. article discussed at p. 49 of the instant specification. These patents disclose administering "protein stabilizing agents" at very high doses, rendering them physiologically infeasible for treating cancer in human patients.